according to claim 69] or a pharmaceutically acceptable salt thereof.

Claim 86, line 2, after "administering" add -- to said mammal --.

Claim 87, line 2, after "administering" add -- to said mammal --.

Kindly add the following claim:

-- 89. 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof.--

ABSTRACT OF THE DISCLOSURE:

Page 121, delete everything after the title up to and including numbered line 18, and substitute the following therefor:

-- 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof has potent angiotensin II --

REMARKS

Favorable and early consideration of the captioned application are courteously solicited in view of the above amendment and these Remarks.

The claims are 70, 71, 77-79, 85-87 and 89.

Claim 69 has been rewritten in independent form as new claim 89. Minor and self-evident wording changes have been made in the remaining claims now before the Examiner for consideration

in the merits, including the presentation of claim 77 and 85 in independent form.

All claims in this application are focused upon the compound 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate which is either expressed as the compound, per se, as in claim 89, or in various *forms* of the compound (claims 70 and 71), or in terms of pharmaceutical compositions based upon this compound (claims 77-79) or the method of use of this same compound, as in claims 85-87. The method of use that is the focus of this invention is the "method for antagonizing angiotensin II in a mammal which comprises administering to said mammal a therapeutically effective amount of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof" as expressed in claim 85.

Changes have been made throughout the specification to delete matter that is directed to compounds other than 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate, without prejudice to protection for the invention as to such compounds or their use.

In amplification of the Information Disclosure Statements already of record, it is noted that there are significant structural differences between 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate of the present invention and, for example, the general disclosure of Carini, U.S. Patent 4,880,804 ("Carini").

As seen from the Carini disclosure and claim 1 a broad range of compounds are generically recited which, when the proper "R" and

other groups are selected, includes within its scope 2-alkoxy*alkyl*-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acids. By picking and choosing the correct substituents, one comes up with compounds which are 2-R^3-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acids, wherein the R^3 group is defined as being any of:

> alkyl of 1 to 6 carbon atoms, alkenyl or alkynyl of 3 to 6 carbon atoms each of which may be unsubstituted or substituted with a halogen atom, $-OR^4$ or $-CO_2R^4$; with the proviso that when R^3 is methyl it must be substituted with $-OR^4$ or $-CO_2R^4$.

Since R^4 is defined as "H, alkyl or 1 to 5 carbon atoms [or other groups]", the group R^3 includes, e.g., ethoxymethyl. Plugging into the various options for the "A" group as -COOH (this selection involves selecting A as $-COR^5$, then selecting $R^5 = OR^6$, and finally R^6 = H); B = R^2 = H; X = "carbon-carbon single bond" and R^1 = 1H-tetrazol-5-yl, this yields within the formula the compound 2-ethoxymethyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid.

The teaching in Carini *away* from 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate is further manifested by looking to what *is* in fact taught by this reference by way of examples, prophetic, working or otherwise. Only Examples 55-64, 71, 72 and 75 are 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazoles as required to match one *part* of the instant 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-*1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole*-7-carboxylate, and of these there is not one single example which is a 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid. Indeed, in no case is any of the 1-[[2'-(1H-tetrazol-5-

yl)biphenyl-4-yl]methyl]benzimidazoles substituted at the 7-position, i.e., the compounds show various 5- or 6-substituted-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazoles and in no event a 7-substituted-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole. Furthermore, the 5- or 6-position substituents are never either the free acid (-COOH) or any ester thereof.

It is manifest that the disclosure of Carini is too nebulous and without direction to this hypothetically achieved 2-ethoxymethyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic so that this particular acid is not, itself, even prima facie suggested under 35 USC § 103.

However, even assuming, arguendo, a suggestion that reached as far as the acid, the acid is not the subject of the instant application, but rather the instant claims are to the 1-(cyclohexyloxycarbonyloxy)ethyl ester of this Carini-hypothetically reconstructed compound. Thus, even if the various "R" groups were plugged together in a manner to suggest the noted acid, there is nothing that would lead to the 1-(cyclohexyloxycarbonyloxy)ethyl ester.

Accordingly, there is an absence of a prima facie case of obviousness as to the compound 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate either as such (in claim 89) or in various stable forms (as in claims 77 and 78) or to compositions (claims 77-79) or methods of use (claims 85-87) based thereon.

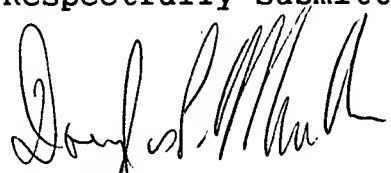
Applicants are not unmindful of the existence of Camara et al, ser. no. 504,441, assigned to Merck ("Camara"), which has been made available to the applicants through observation of the foreign

counterpart application and inspection of the U.S. priority document therein (as well as a second, and presumably now abandoned application, Charavarty et al, ser. no. 351,508, assigned to Merck ("Chakravarty"). Even assuming, arguendo, grant of a U.S. patent that would trigger an issue of 35 USC §§ 102(e), 103, it is seen that the instant compound is legally too remote from the Camara (or Chakravarty) disclosures for there to be a prima facie case of obviousness. In order to find any event remote relevance for Camara or Chakravarty, it is necessary to pick and choose from numerous various in Markush menu listings covering many pages. Even if one in hindsight did so, it should be noted that the hindsight route to *remotely related* compounds is at best tortuous. In Chakravarty one would need to pick and choose for R^{8a} or R^{8b} as $COOR^4$, but R^4 is limited in the Chakravarty claim 1 to the case where R^4 is hydrogen, alkyl of up to six carbon atoms ("straight or branched"), benzyl or phenyl. The 2-position is arrived at by choosing for R^6 the parameter subgrouping "(b)" as an alkyl group, namely, ethyl, and the parameter "E" is selected as -O-. There is no way that one is in any way led to any compound in Chakrvarty (or Camara) with a 1-(cyclohexyloxycarbonyloxy)ethyl ester that would be necessary to reconstruct applicants' compounds even in the bright light of hindsight. The remoteness and *teaching away* is manifested by the disclosure in Chakravarty where there is no relevant disclosure of a substituent at the 7-position. Neither is there a disclosure of any 2-alkoxy-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole. Thus, Example 11 (page 53) discloses 2-butyl-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole; Example 12 (page 56) discloses 2-butyl-4-methyl-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole; Example 13 (page 56) discloses 2-propyl-4-methyl-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole; Example 14 (page 57) discloses 2-butyl-5-carbomethyl-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole; Example 15 (page 57) discloses 2-butyl-

7-hydroxymethyl-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole; Example 16 (page 58) discloses 2-butyl-5-hydroxymethyl-1-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazole. Tabulated as paper experiments in Table I are further 2-alkyl-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}benzimidazoles which are substituted by a variety of groups on the carbocyclic ring of the benzimidazole nucleus by a variety of groups including 5-methyl (page 61, Table 1, second compound); *id.*
(page 61, Table 1, third compound); 7-methyl (page 61, Table 1, penultimate compound); 5-methyl-6-hydroxymethyl (page 61, Table 1, last compound); *id.* (page 62, Table 1, line 2); and so forth.
One compound where the 2-position group is methylthio is tabulated in the paper example at page 62, line 2. In no case is there a single 1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid, either in the working or paper examples.

An action on the merits is courteously solicited.

Respectfully submitted,



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